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(54) Title: ORTHOSTATIC LAVAGE SOLUTIONS

(57) Abstract

The present invention provides a formulation for colon evacuation or for treatment of bowel diseases and/or disorders characterized in that it contains ascorbic acid or a salt thereof, with the proviso that, due to problems of instability, in a dry formulation, the ascorbic acid is packaged separately from the other components or coated. The formulation may be used in a method of whole bowel irrigation or in the treatment of bacterial or inflammatory bowel diseases.

UNIQUEMENT A TITRE D'INFORMATION

Codes utilisés pour identifier les Etats parties au PCT, sur les pages de couverture des brochures publiant des demandes internationales en vertu du PCT.

AT	Autriche	FR	France	ML	Mali
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ORTHOSTATIC LAVAGE SOLUTIONS

TECHNICAL FIELD

The present invention relates to orthostatic lavage solutions or colon evacuants for cleansing the gastrointestinal tract, or for treatment of bowel diseases and/or disorders.

BACKGROUND ART

Orthostatic lavage solutions or colon evacuants for cleansing the gastrointestinal tract were introduced into medical practice only within the last five years. The available solutions which seek to produce volumogenic diarrhoea by ingestion of relatively large volumes of electrolyte solution are almost all identical in their contents of salts, formulated so that they are relatively isotonic, and include poorly absorbable polyethylene glycol. Solutions which are commonly employed include 0.9% sodium chloride, balanced electrolyte solutions, lactated Ringers, mannitol and polyethylene glycol containing electrolyte solutions.

These solutions induce copious diarrhoea when the volume of the solution is greater than the bowel's capacity to distend and absorb it. Generally about 4 to 5 litre of the solution is necessary to obtain adequate cleansing of the gastrointestinal tract for colonoscopy or bowel surgery. Apart from the necessary diarrhoeagenic effect, the large volume required and the particularly unpleasant taste of the solutions contribute to the chief side effects of nausea and vomiting. These side effects are counter productive in reaching the desired aim of complete and rapid purging and cleansing of the bowel. The unpalatability of the solutions also result in poor patient compliance.

Flavouring the currently used solution with standard agents is difficult due to the large destabilizing amount of flavouring agents required to block the unpleasant nauseating taste of salts. Sugar based flavours are not acceptable since delivery of unabsorbed sugars to the colon provides a substrate for bacteria to elaborate explosive gases such as hydrogen and methane. In fact, recent studies (J. Crowe et al.[1]) have indicated that even the unflavoured polyethylene glycol solutions currently in use may create hydrogen and methane in potentially explosive concentrations when cautery is used within the colon.

Furthermore, most bowel preparations using orthostatic lavage precede either colonoscopy or bowel surgery with a lesser usage in barium-enema bowel radiology. Since patients requiring such procedures are usually in the older age group and may be candidates for surgery after discovery of a bowel cancer, for example, it would be of advantage if the solution had

bacteriocidal properties and/or could simultaneously replace nutrients necessary for repair.

Therefore it would be desirable to provide a colon evacuant wherein the unpleasant taste of the normally used isotonic solutions containing PEG is masked, wherein it has endogenous diarrhoea producing properties, and wherein it confers bacteriostatic of bacteriocidal properties to reduce bowel gas production or post-operative infection and yet can replace some nutrient value pre-operatively.

It is an object of the present invention to provide an agent which may be combined with flavouring and sweetening agents, which significantly reduces the potential for explosion due to a reduction of explosive gasses secondary to a bacteriostatic effect on bowel bacteria, and which allows a reduction in the volume of standard lavage solutions containing polyethylene glycol by at least about 25%.

Thus providing a more palatable and effective formulation, with fewer side effects, greater patient compliance and less risk of explosion.

DISCLOSURE OF THE INVENTION

The present invention provides a formulation for colon evacuation or for treatment of bowel diseases and/or disorders characterized in that it contains ascorbic acid or a salt thereof. Because of the poor stability of ascorbic acid in solution, it should be packaged separately from the other components of the formulation or coated in dry formulations. In liquid formulations, it should not be added until just before use.

The formulations of the present invention may also contain electrolytes, for example, those having an isotonic profile. The formulations may also contain sweetening and/or flavouring agents.

If uncoated ascorbic acid is employed in the formulations of the invention it can cross react in the dry form with other components of the formulation.

The present inventor has found that the addition of ascorbic acid in larger than usual doses to typical lavage solutions tends to reduce the required volume for satisfactory colon evacuation. With the typical polyethylene glycol electrolyte lavage solutions, the required volume for appropriate colon preparation is about 4 litre. The addition of ascorbic acid to the lavage solution has been shown to reduce the required volume to about 3 litre or less.

The present invention also provides a method of whole bowel irrigation wherein a volume of about 2 to 3.5 litre of a lavage solution of the present invention is administered over a period of time to induce

volumogenic diarrhoea. Generally this period of time will be about 1.5 to 4 hours.

BEST MODES OF CARRYING OUT THE INVENTION

In the preferred formulations of the present invention, ascorbic acid is incorporated in larger than usual oral concentrations to give a composition in the lavage solution of between about 0.25 to 50g/l, especially 1 to 25 g/l for colon evacuants or 20 to 35 g/l for treatment of bowel diseases and/or disorders. Since only a single dose is given during the lavage and the human intestine is capable of absorbing at most about 3g of ascorbic acid (Hornig D. et al.[2]), the remainder of the dose contributes to the diarrhoea and inhibits bacterial gas generation and reproduction. The excess ascorbic acid is passed without doing harm to the patient whilst the absorbed quantity is available as a specific nutrient and could be advantageous in the post-operative healing stage.

Typically, lavage solutions are provided in powdered form which are reconstituted to the required volume immediately prior to use. The lavage solutions of the present invention when made up ready for use will generally contain at least about 0.25g/l ascorbic acid. More preferably they will contain from 5 to 50g per 3 litre of solution when made up, more preferably about 20g per 3 litre when made up.

For dry formulations the ascorbic acid must be coated. Silicone or ethyl cellulose form suitable coatings to prevent reaction between the ascorbic acid and other components of the formulation.

Suitable coated ascorbic acid is available from Roche Products Pty Ltd as Coated Ascorbic Acid, Type EC and Coated Ascorbic Acid, Type SC.

Preferred lavage solutions of the present invention also contain high molecular weight polyethylene glycol such as polyethylene glycol having molecular weights greater than about 2000. Preferred polyethylene glycol has a molecular weight of about 3000 to 4500 such as PEG 3350, or PEG 4000.

Preferred lavage solutions of the present invention also contain a number of electrolytes and preferably have an isotonic electrolyte profile.

Preferred solutions have the following constituents in the range as specified.

	RANGE OF CONCENTRATION g/litre H_2O of made up solution
Polyethylene glycol	30 - 60
Sodium chloride	0.5 - 3.0
Potassium chloride	0.2 - 2.0

Sodium hydrogen carbonate	0.5	-	5.0
Sodium sulfate (anhydrous)	2.0	-	10.0
Ascorbic acid	0.25	-	50.0

Preferably, the polyethylene glycol in the standard lavage solutions is adjusted so as to result in an osmolality of approximately 289m osm/ litre.

It is also possible to add flavourings to the lavage solutions of the present invention so long as these flavourings are not metabolized to an explosive gas such as hydrogen or methane in the bowel. For example aspartame may be added in a concentration of about 0.05 to 1%. Lemon flavour (SD - Natural lemon powder flavour No. 12606) or pineapple flavour (10966) may also be added at concentrations of 0.5 to 4.0% or cyclamates may be added to increase the palatability of the lavage solution.

The lavage solutions of the present invention are also useful in the treatment of certain gastrointestinal conditions such as small bowel bacterial overgrowth and irritable bowel syndrome as well as useful in treating acute or chronic bacterial bowel infections, for example, infection of the bowel with one or more bacteria including Campylobacter jejuni, Yersinia enterocolitica, Clostridium difficile, Cryptosporidium isospora belli. The lavage solutions of the present invention can also be used in the treatment of chronic inflammatory bowel disease such as Crohns disease or ulcerative colitis. In treating these conditions, ascorbic acid or its salts is used in a wide range of concentrations depending on the specific condition and may vary from about 1g to about 50g per litre, preferably from 20g to 35g per litre. Therefore, the lavage solutions useful in methods to treat the acute or chronic bacterial bowel infections or chronic inflammatory bowel disease will contain ascorbic acids or a salt thereof in a range so that when made up as ready for ingestion, the concentration of ascorbic acid will be from about 1 to 50g per litre. These lavage solutions useful in these treatments will also preferably be isotonic and include high molecular weight polyethylene glycol.

The invention will further be described by reference to the following examples.

EXAMPLE 1

A solution having the following composition was made up:

	g/L Water
Polyethylene glycol	54
Sodium chloride	1.46

Potassium chloride	0.745
Sodium hydrogen carbonate	1.68
Sodium sulfate	5.68
Ascorbic acid	6.6

A total of 3 litre was administered to the patient over 2 to 5 hours and the bowel preparation quality was found to be comparable to that requiring 4 litre of the standard available preparation. Ingestion was greatly facilitated due to the pleasant acidic taste which masked the usual nauseating taste of the salty polyethylene glycol solution. Colon hydrogen levels were acceptably low. Biopsies of colon obtained from the ascending transverse and descending colon sites were normal and without mucosal oedema.

EXAMPLE 2

A solution having the following composition was made up and administered as in Example 1.

	g/L Water
Polyethylene glycol	38
Sodium chloride	0.95
Potassium chloride	1.63
Sodium hydrogen carbonate	3.42
Sodium sulfate	2.75
Ascorbic acid	25
Lemon flavour	7.5

EXAMPLE 3

A solution having the following composition was made up and administered as in Example 1.

	g/L Water
Polyethylene glycol	49
Sodium chloride	2.4
Potassium chloride	1.2
Sodium hydrogen carbonate	2.82
Sodium sulfate	7.41
Ascorbic acid	37.1
Pineapple flavour	9.0

EXAMPLE 4

A solution having the following composition was made up and administered as in Example 1.

	g/L Water
Polyethylene glycol	32
Sodium chloride	0.6
Potassium chloride	0.23
Sodium hydrogen carbonate	0.65
Sodium sulfate	2.25
Ascorbic acid	0.8
Cyclamate	0.5

EXAMPLE 5

A solution having the following composition was made up and administered as in Example 1.

	g/L Water
Polyethylene glycol	57
Sodium chloride	2.7
Potassium chloride	1.8
Sodium hydrogen carbonate	4.45
Sodium sulfate	9.5
Ascorbic acid	46.5
Aspartame	9.0

EXAMPLE 6

A dry formulation having the following composition was made up:

	Kg
Potassium chloride	2.092
Sodium chloride	4.127
Sodium hydrogen carbonate	4.748
Sodium sulphate (Anhydrous)	16.054
Ascorbic acid (Silicone coated)	16.959
Lemon flavour 12606	2.826
Aspartame	.565
Polyethylene glycol 4000	152.629
	Total 200.000

EXAMPLE 7

A dry formulation having the following composition was made up:

Potassium chloride	2.092	Kg
Sodium chloride	4.127	
Sodium hydrogen carbonate	4.748	
Sodium sulfate (Anhydrous)	16.054	
Ascorbic acid (Silicone coated)	16.959	
Pineapple flavour 10966	1.979	
Aspartame	.565	
Polyethylene glycol 4000	152.629	
	Total 199.153	

Individual doses of the dry formulations were made up to a volume of 3 litre with water, and the resultant solution was kept cold to increase palatability. The solution was administered to the patient over a period of 1 to 5 hours.

The formulation may be packaged for single applications in sachets, plastic bags or in a 3-4 litre jug to which water may be added to be made up to a specific volume. Alternatively the formulation may be packaged in screw top boxes or cartons, preferably with an air tight seal. Vitamin C can be kept separately in an air tight sachet to be added at the time of mixing particularly if it is uncoated by ethyl cellulose or silicone. It can also be packaged in sachets lined by agents such as Mylar to prevent water absorption.

REFERENCES

1. J. Crowe et al.; A Study of Intracolonic Hydrogen and Methane Concentrations in Patients. GUT 1987; 28: A1370.

2. Hornig D. et al.; Int. J. Vit. Nutr. Res. 1980; 50: 309.

ORTHOSTATIC LAVAGE SOLUTIONS

CLAIMS

1. A formulation for colon evacuation or for treatment of bowel diseases and/or disorders characterized in that it contains ascorbic acid or a salt thereof, with the proviso that in a dry formulation, the ascorbic acid is packaged separately from the other components or coated.

2. The formulation according to claim 1, provided in solution.

3. The formulation according to claim 1, wherein the concentration of ascorbic acid is about 0.25 to 50g/l.

4. The formulation according to claim 1, or wherein the concentration of ascorbic acid is about 1 to 25g/l.

5. The formulation according to claim 1, wherein the concentration of ascorbic acid is about 20 to 35g/l.

6. The formulation according to claim 1, which contains at least one electrolyte.

7. The formulation according to claim 6, wherein said electrolyte has an isotonic profile.

8. The formulation according to claim 6, wherein said electrolyte is selected from the following: sodium chloride, potassium chloride, sodium hydrogen carbonate, sodium sulfate.

9. The formulation according to claim 1, which contains high molecular weight polyethylene glycol.

10. The formulation according to claim 9, wherein said polyethylene glycol has a molecular weight greater than about 2000.

11. The formulation according claim 10, wherein said polyethylene glycol has a molecular weight of about 3000 to 4500.

12. The formulation according to claim 9, wherein the polyethylene glycol is present in an amount so as to result in an osmolality of about 289m osm/l.

13. The formulation according to claim 1, further comprising sweetening and/or flavouring agents not metabolized to an explosive gas.

14. The formulation according to claim 13. wherein said sweetening agent and/or flavouring agent is selected from the following: aspartame, pineapple flavour 10966, lemon flavour 12606 or cyclamates.

15. A formulation for colon evacuation or for treatment of bowel diseases and/or disorders, characterised in that it has the following composition: polyethylene glycol 30-60, sodium chloride 0.5-3.0, potassium chloride 0.2-2.0, sodium hydrogen carbonate 0.5-5.0, sodium sulfate (anhydrous) 2.0-10.0, ascorbic acid 0.25-50.0; g/l of water.

16. A formulation for colon evacuation or for treatment of bowel diseases and/or disorders, characterised in that it has the following composition: polyethylene glycol 54, sodium chloride 1.46, potassium chloride 0.745, sodium hydrogen carbonate 1.68, sodium sulfate (anhydrous) 5.68, ascorbic acid 6.6; g/l of water.

17. The formulation according to claim 1, provided in powdered form.

18. The formulation according to claim 17, wherein the ascorbic acid is coated with silicone or ethyl cellulose.

19. A method of whole bowel irrigation wherein a volume of about 2 to 3.5 litres of a formulation according to claim 1, is administered over a period of time to induce volumogenic diarrhoea.

20. A method according to claim 19 wherein the formulation is administered over about 1.5 to 4 hours.

21. A method of treating small bowel bacterial overgrowth or irritable bowel syndrome, in a patient requiring said treatment, which method comprises administering to said patient an effective amount of a formulation according to claim 1.

22. A method of treating acute or chronic bacterial bowel infection, in a patient requiring said treatment, which method comprises administering to said patient an effective amount of a formulation according to claim 1.

23. A method according to claim 27, wherein said infection is caused by at least one of the following: Campylobacter jejuni, Yersinia enterocolitica, Clostridium difficile, Cryptosporidium isospora belli.

24. A method of treating chronic inflammatory bowel disease, in a patient requiring said treatment, which method comprises administering to said patient an effective amount of a formulation according to claim 1.

25. A method according to claim 24, wherein the inflammatory bowel disease is Crohns disease.or Ulcerative colitis.

INTERNATIONAL SEARCH REPORT

International Application No PCT/AU 88/00484

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl.[4] A61K 47/00 // A61K 31/045

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC	A61K 47/00, 31/045, 31/375

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

AU : IPC as above; Australian Classification 87.16-0 (SF120)

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	AU,B, 73343/81 (544544) (ERWIN GUNTHER WALLICZEK) 25 February 1982 (25.02.82) See especially page 2 lines 1-15, and page 5 lines 7-12.	(1)
P,Y	AU,A, 13063/88 (HAMILTON D.S.) 15 September 1988 (15.09.88)	(1)
P,Y	WO,A, 88/08715 (PROCYTE CORP.) 17 November 1988 (17.11.88)	(1)
A	AU,B, 30504/84 (569747) (UNIV. OF SOUTHERN CALIFORNIA) 17 January 1985 (17.01.85)	(1)
A	Patents Abstracts of Japan, C-20, page 338 JP,A, 59-81648 (KAO SEKKEN K.K.) 9 November 1985 (09.11.85)	(1)

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
6 April 1989 (06.04.89)	18 APRIL 1989 (18.04.89)
International Searching Authority: Australian Patent Office	Signature of Authorized Officer: J.P. PULVIRENTI

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 19-25 because they relate to subject matter not required to be searched by this Authority, namely:

Method of treatment of the animal body by therapy.

2. [ ] Claim numbers ....., because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers ....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON
INTERNATIONAL APPLICATION NO. PCT/AU 88/00484

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Members		
AU 73343/81	EP 46409	JP 57075914	
AU 13063/88	ZA 8801828		
WO 8808715	AU 17995/88		
AU 30504/84	CA 1237988 GB 2144990 US 4504493	DE 4535745 IL 72355	FR 2548897 JP 60100514
JP 59-81648	JP 60224614 JP 62240441	JP 61240285 US 4729358	EP 241029 JP 63246133

END OF ANNEX